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Multimodality Treatment of Noninflammatory Stage IIIb Breast Cancer

BOGDAN GLIŃSKI, MD,[1]* MAREK PAWLICKI, MD,[2] MARIAN REINFUSS, MD,[1] JAN SKOŁYSZEWSKI, MD,[1] ANNA BRANDYS, MD,[2] KRZYSZTOF KRZEMIENIECKI, MD,[2] BEATA ŻUCHOWSKA, MD,[2] JERZY MITUŚ, MD,[3] ANDRZEJ STELMACH, MD,[3] AND TOMASZ WALASEK, MD[1]

[1]*Department of Radiotherapy, Maria Sklodowska-Curie Memorial Center of Oncology, Cracow, Poland*

[2]*Department of Medical Oncology, Maria Sklodowska-Curie Memorial Center of Oncology, Cracow, Poland*

[3]*Department of Surgical Oncology, Maria Sklodowska-Curie Memorial Center of Oncology, Cracow, Poland*

Background and Objectives: The 1990s have established the contribution of multimodality therapy in the management of IIIb noninflammatory breast cancer (IIIb NIBC), by reducing the odds of recurrence and death.
Methods: A total of 300 women with IIIb NIBC received a multimodality therapy. The treatment consisted of neoadjuvant chemotherapy [FAC (5-fluorouracil, Adriamycin, cyclophosphamide) regimen], radical (Halsted) mastectomy or modified (Patey mastectomy), postoperative radiotherapy, and adjuvant chemohormone therapy [FAC regimen + cyclophosphamide, 5-fluorouracil and methotrexate (CMF) regimen or Tamoxifen].
Results: Complete or partial clinical response (CR or PR) after neoadjuvant chemotherapy was obtained in 83% patients. Ninety-nine patients (33%) survived 5 years without evidence of disease (NED). The uni- and multivariate analyses factors that had significant influence on the treatment results were: clinical response to neoadjuvant chemotherapy, pathological tumor size, and microscopical status of the axillary lymph nodes.
Conclusions: We conclude that neoadjuvant FAC regimen chemotherapy is very effective in producing objective tumor regression and offers the benefit of radical mastectomy to patients with previously unresectable IIIb NIBC. *J. Surg. Oncol. 1997;66:179–185.*

KEY WORDS: **neoadjuvant chemotherapy; breast cancer; surgery; radiotherapy**

INTRODUCTION

Stage IIIb breast cancer patients generally are considered to be primarily inoperable, and multimodality therapy with initial chemohormone therapy followed by locoregional treatment has become increasingly popular during the two past decades [1–11]. Since 1970 in our institute, treatment consisting of neoadjuvant chemotherapy, radical mastectomy, postoperative radiotherapy, and adjuvant chemohormone therapy has been standard for patients with locally advanced breast cancer [12]. This study presents our experience with this triple-modality therapy of patients with noninflammatory stage IIIb breast cancer.

MATERIALS AND METHODS

Between January 1980 and December 1990, 451 previously untreated women with stage IIIB breast cancer were seen at the Center of Oncology in Cracow. Inflammatory carcinoma was diagnosed in 122 (27.0%) patients. Six (1.3%) women refused therapy, 12 (2.7%) were qualified to receive palliative monochemohormone therapy or symptomatic care only because of

*Correspondence to: Dr. Bogdan Gliński, M.D., Department of Radiotherapy, Maria Sklodowska-Curie Memorial Center of Oncology, Garncarska 11, 31115, Cracow, Poland.

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old age and/or intercurrent disease, and 11 women (2.4%), with the presence of locoregional progression and distant metastases during the neoadjuvant chemotherapy, were treated subsequently with other chemotherapy regimens, hormone therapy, or palliative radiotherapy. We further analyzed the remaining 300 (66.6%) patients with stage IIIB noninflammatory breast cancer (IIIB NIBC) treated with multimodality therapy (neoadjuvant chemotherapy, surgery, postoperative radiotherapy, and adjuvant chemohormone therapy). Their ages ranged from 36 to 70 years, (mean 54 years). A total of 154 patients (51.3%) were >55 years of age; 118 (39.3%) patients were premenopausal; 72 (24%) patients were perimenopausal (<5 years from the last period); and 110 (36.7%) patients were postmenopausal (>5 years from the last period). Duration of symptoms varied from 1 to 24 months, the mean being 7 months. The diagnosis of cancer was made by incisional biopsy, or, since 1986, by needle biopsy. Infiltrating ductal carcinoma was found in 261 (87%) patients and other histologic types of invasive breast carcinomas in 39 patients (13%).

Patients were jointly evaluated and staged by the staff of the Radiotherapy, Medical Oncology, and Surgical Oncology departments. Pretreatment diagnostic procedures included a careful history and complete physical examination, routine biochemical analyses (renal and liver function tests), complete blood count, electrocardiogram, and, since 1987, mammography. Distant metastases were excluded by chest X-ray, bone scan, and liver scan and/or ultrasonography. All patients had a Karnofsky index of at least 80, adequate renal and hepatic function, no history of myocardial infarct or congestive heart failure or cardiac arrythmias, white blood cell count >4,000/ml, and platelet count >150,000/ml. Estrogen and progesterone receptors assays were not specified in our center until 1990.

All patients were staged retrospectively according to the American Joint Committee on Cancer (AJCC) TNM 1993 classification [13] and the presented group of 300 patients included 80 T4a (26.7%), 162 T4b (54.0%), and 58 T4c (19.3%) patients; clinically 6 (2%) patients were N0, 45 (15%) N1, and 249 (83%) N2. The tumor size ranged from 4 cm to 18 cm, the mean being 9 cm. Tumors <5 cm were found in 5 (1.7%) patients, 5–10 cm in 115 (38.3%) patients, and >10 cm in 180 (60%) patients.

The treatment was begun with chemotherapy. All patients received FAC regimen (5-fluorouracil 500 mg/m^2, days 1 and 8, Adriamycin 50 mg/m^2, day 1, cyclophosphamide 500 mg/m^2, day 1). The course was repeated every 21 days; 270 (90.0%) patients received four courses and 30 (10.0%) patients received five courses. Response to neoadjuvant chemotherapy was evaluated by physical examination and mammography (since 1987) before each course of chemotherapy. After four or five courses of chemotherapy, patients were evaluated by the joint planning staff.

In all our patients, surgical treatment was performed after neoadjuvant chemotherapy. Radical Halsted mastectomy was carried out in 234 (78%) cases, and modified Patey mastectomy in 66 (22%) cases.

A total of 216 (72%) patients received postoperative irradiation. Radiotherapy was administered with a Cobalt 60 machine with a tumor dose of 5,000 cGy in 25 fractions over 5 weeks to the chest wall and the internal mammary, supraclavicular, and axillary areas. In six T4a patients, the radical (Halsted) mastectomy was not microscopically complete in the area of the chest wall. These microscopically suspicious areas received an additional 1,000–1,500 cGy, using 15 MeV electron beam, to restricted fields. Twenty-one (19%) patients with no histologic evidence of residual tumor (pT0, pN0) were not irradiated postoperatively. Sixty-three (21%) patients did not receive postoperative radiotherapy, because of refusal (20 patients), or logistic problems concerning therapy (43 patients).

Immediately following completion of local therapy, chemotherapy according to the FAC regimen was reinstituted until a total cumulative dose of 450 mg/m^2 Adriamycin was reached. After Adriamycin was discontinued, pre- and perimenopausal patients received the CMF regimen (cyclophosphamide 500 mg/m^2, day 2; 5-fluorouracil 500 mg/m^2, days 1 and 8; methotrexate 30 mg/m^2, days 1 and 8). The courses were repeated every 21 days, and the therapy was continued for 6 months. Postmenopausal patients received hormonetherapy—Tamoxifen (™) 20 mg/d for 2 years or until progression.

RESULTS

All patients were followed for at least 5 years. Every 3 months they had a physical examination, routine biochemical analysis, and complete blood count, and every 6 months chest X-ray, a bone scan, and abdominal ultrasonography were carried out. After local recurrence or the appearance of distant metastases, patients were treated with chemohormone therapy, or debulking surgery and palliative radiotherapy.

Five-year survival without evidence of disease (NED) was used as the end-point for analysis. The survival time was calculated from the date of the first day of neoadjuvant chemotherapy. Statistical significance of observed differences was set up at $P < 0.05$ and determined by the log-rank test [14]. Multivariate analysis was conducted by the Cox proportional hazard model to identify the onset of independent prognostic factors for 5-year NED survival [15].

It was possible to define three prognostic groups of patients on the basis of their response to the therapy: complete clinical responders (those with no evidence of residual tumor by clinical examination), partial clinical

TABLE I. Clinical Response to Neoadjuvant Chemotherapy in a Group of 300 Patients With IIIb Noninflammatory Breast Cancer

Clinical response	No. of patients (%)
Complete	42 (14.0)
Partial	207 (69.0)
Stable disease	51 (17.0)
Total	300 (100.0)

responders (those with ⩾50% reduction in the clinical tumor size), and patients with stable disease (those with <50% reduction, without increase in clinical tumor size). Clinical response to the therapy is shown in Table I.

Complete or partial clinical response was obtained in 249 patients (83%); in 51 (17%) patients stable disease was observed. No progression of disease was noted.

Pathological examination of the operated materials found tumors >5 cm in 41 patients (13.7%) only. Metastases to axillary lymph nodes were found in 279 (93%) patients. In 21 patients (7.0%), the pathologic complete response of disease (pT0, pN0) was obtained after the neoadjuvant chemotherapy [Table II].

Of the 300 patients in the group treated with multimodality therapy (neoadjuvant chemotherapy + surgery ± radiotherapy, and adjuvant chemo- or hormone-therapy), 99 (33.0%) survived 5 years NED. The age of patients, duration of symptoms, menopausal status, and histologic type of carcinoma did not appear to influence significantly the treatment results. Table III shows the results according to clinical and pathological features.

In the univariate analysis, no statistically significant relationship between treatment results and the clinical T and N status, type of surgery, and application of postoperative radiotherapy was found. Of significant influence on the treatment results in the uni- and multivariate analysis were: clinical response to neoadjuvant chemotherapy, pathological tumor size (pT), and microscopical status of axillary lymph nodes. Survival curves considering these three features, are presented in Figures 1, 2, and 3; the differences are statistically significant (log-rank test, $P < 0.01$, $P < 0.02$, $P < 0.01$, respectively).

Of the 21 women with no histologic evidence of residual tumor (pT0, pN0), 17 patients (81%) survived 5 years NED. The results of the follow-up of our patients are presented in Table IV.

During the 5-year follow-up period, two women died of myocardial infarction and one died of cerebral hemorrhage. Seven of our patients who survived 5 years with cancer died from 6 to 8 years after the treatment. Of 198 patients with persistent cancer, 190 patients (96%) died of distant metastases to bones, lungs, liver, and brain, and only 8 patients (4%) died of locoregional failure.

The multimodal therapy was well tolerated in our group of patients. No treatment related deaths were observed. After chemotherapy nausea, vomiting, myelosuppression, and alopecia grade 1, according to the classification of Miller et al. [16] were presented in most patients, but were completely reversible. Myelosuppression grades 2 and 3 was observed in 12 (4%) of patients: neutropenia (<1,000/ml), managed by ambulatory antibiotics, in 10 patients, whereas sepsis and aplasia required hospitalization in 2 patients. Three patients developed congestive heart failure during the treatment, which was controlled by digitalis and diuretics.

TABLE II. Pathological Tumor Size (pT) and Microscopical Status of Axillary Lymph Nodes (pN) in a Group of 300 Patients With IIIb Noninflammatory Breast Cancer

Pathologic characteristics	No. of patients (%)
Tumor size (pT)	
T0	21 (7.0)
<2cm	46 (15.3)
2–5 cm	192 (64.0)
>5cm	41 (13.7)
Status of axillary lymph nodes (pN)	
negative (N0)	21 (7.0)
positive (N+) 1–3	104 (34.7)
>3	175 (58.3)

TABLE III. Results of Multimodality Therapy of 300 Patients With IIIb Noninflammatory Breast Cancer

Clinicopathologic characteristics	No. of patients	Alive 5-years NED	%
Clinical T status [13]			
T4a	80	26	32.5
T4b	162	55	34.0
T4c	58	18	31.0
Clinical N status [13]			
N0	6	3	50.0
N1	45	16	35.6
N2	249	80	32.1
Response to chemotherapy*			
Complete	42	30	1.4
Partial	207	64	30.9
Stable disease	51	5	9.8
Type of surgery			
modified radical Patey mastectomy	66	23	34.8
radical Halsted mastectomy	234	76	32.5
Postoperative radiotherapy			
yes	216	66	30.6
no	84	33	39.3
Pathological tumor size (pT)*			
pT0	21	17	81.0
<2 cm	46	23	50.0
2–5 cm	192	57	29.7
>5 cm	41	2	4.9
Axillary lymph nodes*			
negative (pN0)	21	17	81.0
positive (N+) 1–3	104	51	49.0
>3	175	31	17.7
Total	300	99	33.0

NED, no evidence of disease.
*Differences statistically significant (log-rank test, $P < 0.05$).

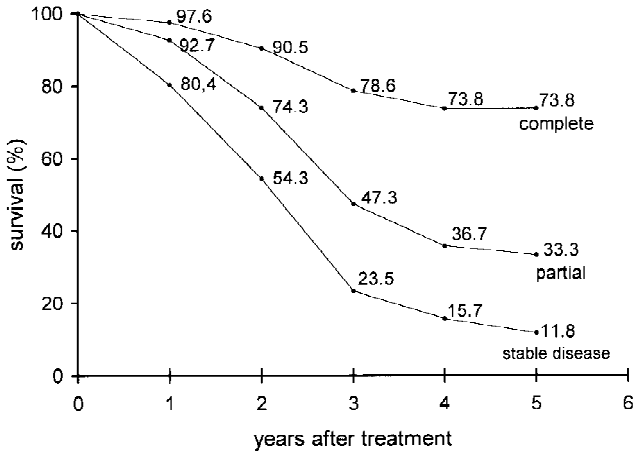

Fig. 1. Correlation between the results and clinical response to neoadjuvant chemotherapy.

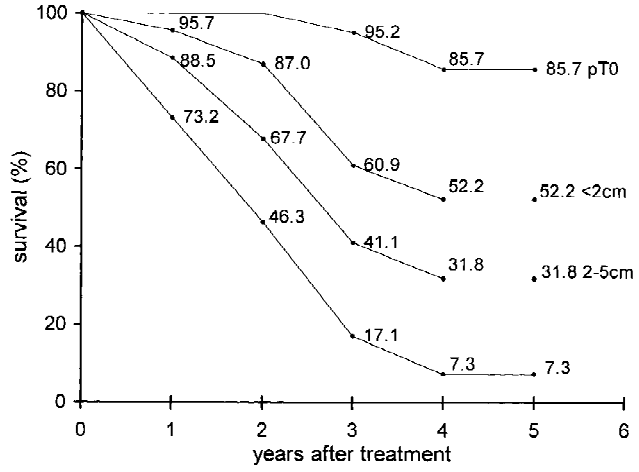

Fig. 2. Correlation between the results and pathological tumor size.

No surgical complication occurred. The combination of axillary dissection and postoperative radiotherapy led to marked arm lymphedema in 15 patients (5%).

DISCUSSION

Our analysis confirmed that neoadjuvant multidrug chemotherapy is very effective in producing objective tumor regression in patients with locally advanced breast cancer. After four or five courses of FAC regimen chemotherapy, 14% of our III B NIBC patients achieved complete clinical response (CR) and 69% had partial response (PR). These results concur with most of those reported in the literature where the CR ranges from 0% to 50%, and PR from 34% to 85% [9,10,17–29]. In 21 patients (7%) of our group, a pathologic complete response of the disease (pT0, pN0) was obtained. This is a percentage comparable to those presented by Gardin et al., 3.5% [10], Cognetti et al., 12% [21], Booser et al., 11% [30], Costa et al., 11.5% [28], but is lower than the

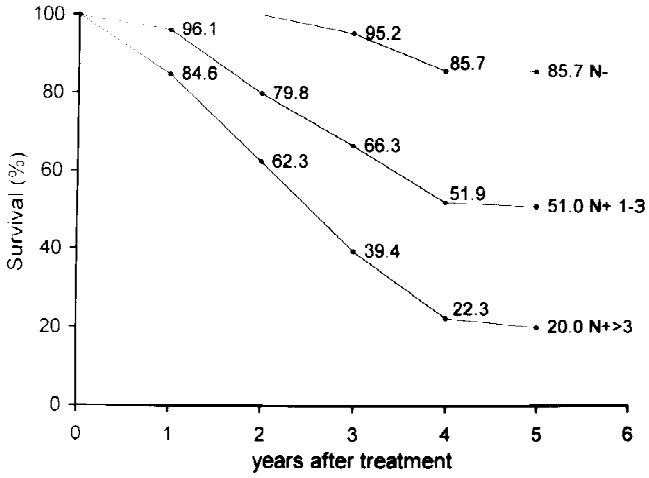

Fig. 3. Correlation between the results and microscopical axillary lymph nodes status.

TABLE IV. Follow-Up of 300 Patients With IIIb Noninflammatory Breast Cancer

Results	No. of patients (%)
5-year no evidence of disease survival	99 (33.0)
5-year survival with cancer	7 (2.3)
Died with cancer during the 5-year follow-up period	191 (63.7)
Died during the 5-year follow-up period for reasons not related to cancer	3 (1.0)
Total	300 (100)

CR shown by Ben-Baruch et al., 29% [23], and Flores et al., 24% [26].

In the literature, 5-year survival in patients with locally advanced breast cancer treated with multimodality therapy (neoadjuvant chemotherapy, surgery, and/or radiotherapy, and eventually adjuvant chemohormone therapy), ranges from 35% to 58%, and 5-year NED survival from 23% to 52% [10,19,20,23,24,27,28,31–37]. Of our group of 300 patients treated with multimodality therapy, 99 patients (33%) survived 5 years NED. Thus our results concur with much of those presented in the literature. Of course, it is very difficult to compare our results of neoadjuvant chemotherapy and multimodality therapy with those of the other authors, because their references include generally joint reports on IIIa and IIIb breast cancer, or IIIb, combining noninflammatory and inflammatory cancer cases, whereas we presented only patients with IIIb NIBC.

The other objective of our study was to discuss the problem of prognostic factors in patients with IIIB NIBC treated with multimodality therapy. In the Cox multivariate analysis of our group, three variables were independently related to survival: clinical response to neoadjuvant chemotherapy, pathological tumor size (pT), and microscopical status of axillary lymph nodes (pN). Prognostic significance of pathological tumor size and axil-

lary lymph nodes in patients with locally advanced breast cancer is generally accepted in literature [1,2,7–10,19,20,32,38–40].

The opinions on correlation between the clinical response to neoadjuvant chemotherapy and the prognosis vary. Some question the existence of this correlation [11,23,41,42], but it was found in the analysis of most authors [3,5,7,17,19,32,34,38,39,43–45]. In the group of 30 women with locally advanced breast cancer treated by Gasparini et al., 3-year survival was 77% for complete responders compared, with 24% for others [34]. Tumor regression after neoadjuvant chemotherapy was also the main predictive factor for disease-free survival in a group of 98 patients presented by Jacquillat et al.; the rate of relapse was 34% for patients with regression >75% and 54% for those with less marked regression [17]. In the group presented by Hortobagyi et al., 5-year NED survival rates for patients with complete response, partial response, no change, and progressive disease were 83%, 36%, 19%, and 0%, respectively [19].

Our results of multimodality treatment of 21 patients with no histologic evidence of residual tumors after neoadjuvant chemotherapy (complete pathological regression—pCR, -pT0, pN0) are very good at 81% 5-year NED survivors. Similar observations have been made by other authors [38,43,45,46]. In the group treated by Sataloff et al. [45], patients with excellent pathologic therapeutic response had a 79% overall 5-year survival rate compared with 34% for tumors with a lesser response. Mc Cready et al. [38] observed that there was little difference in survival between patients who had clinical partial response and those who had no tumor response; however, patients with complete pathologic tumor regression had a 92% 5-year NED compared with 30% in other patients. Feldman et al. [43] presented, based on a group of 90 patients with inflammatory and locally advanced breast cancer, that patients whose mastectomy specimens had no macroscopic residual disease had a 93% 5-year survival compared to patients with a less marked response to therapy who had a 5-year survival of 30%. In a group presented by Hortobagyi et al. [46], the disease-free survival of patients with pCR was projected to be in excess of 60 months, whereas it was only 29 month for patients without pCR.

Other reports point to other pretreatment prognostic factors in patients with locally advanced breast cancer treated with multimodality therapy: age [19], menopause status [38], estrogen and progesterone receptors [2]. These variables were not significant as prognostic factors in our study. Our study shows that the clinical response to neoadjuvant chemotherapy, pathological tumor size (pT), and microscopical status of axillary lymph nodes (pN) significantly affect survival. We did not investigate such new potential prognostic factors as cell kinetics and ploidy, oncogene overexpression, gene amplification, or epidermal growth factor receptor [2,5,21,47–51].

Currently under study in many centers is breast conservation in locally advanced disease in conjunction with neoadjuvant chemotherapy. It appears that in selected subgroups (clinically complete responders?), this approach yields local control and survival rates similar to those attainable with mastectomy and postoperative radiotherapy [1,2,4,6,7,19,30,32,52–55]. Neoadjuvant chemotherapy also has been used for tumors >3 cm in order to render them small enough for lumpectomy [40,56–60].

Despite improvements in multimodality therapy, the predominant cause of failure in locally advanced breast cancer are distant metastases [10,17,19,20,28,32,39,46]. Out of our 198 IIIB NIBC patients with persistent cancer, 190 patients (96%) died of distant metastases to bones, lungs, liver, and brain. Thus eradication of the resistant micrometastatic disease after chemotherapy remains a major problem for most patients with IIIB NIBC treated with multimodality therapy. Perhaps the use of more effective drugs and chemotherapy regimens in neoadjuvant and adjuvant treatment, could improve the survival rate of these patients [2,19,59].

A detailed analysis of our own clinical material, consisting of 300 patients, and a review of the literature allow us to recommend the neoadjuvant FAC regimen chemotherapy as very effective in producing objective tumor regression and offering the benefit of radical mastectomy to patients with previously unresectable IIIB NIBC. Multimodality treatment incorporating the use of neoadjuvant chemotherapy, surgery, postoperative radiotherapy (above 30%), and adjuvant chemo- or hormonetherapy offered a chance of 5-year NED survival to one-third of patients with IIIB NIBC.

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